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Strategies for optimizing hemoglobin response in cancer patients: focus on new epoetin alfa dosing regimens

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Abstract

As the prevalence and impact of anemia in patients with cancer have been recognized, clinical guidelines with recommendations for the use of both transfusions and recombinant human erythropoietin (rHuEPO; epoetin alfa) are continuing to evolve. The strength of recommendations varies depending on the availability of randomized, controlled clinical trial data for a given endpoint, which can include transfusion reduction, improvements in hemoglobin (Hb) levels, quality of life (QOL) improvement, or potential treatment outcome benefits. Clinical studies have shown that epoetin alfa, in doses of 150–300 IU/kg three times a week, consistently increases Hb levels by ~1 g/dl at 4 weeks and ~2 g/dl at 8 weeks. A prospective, community-based clinical trial has demonstrated that a once-weekly (QW) regimen of epoetin alfa (40 000–60 000 IU) increases Hb levels by 1.1 g/dl at week 4 and by 1.7 g/dl at week 8. Results from a second prospective, open-label, community-based trial are consistent with these findings. These increases are associated with statistically significant reductions in transfusion requirements and improvements in QOL. The question as to whether epoetin alfa should be given to patients with mild anemia is currently being evaluated in several early-intervention studies (i.e. in patients with mean Hb ~12 g/dl). Preliminary results suggest that epoetin alfa, given QW at doses of 40 000–60 000 IU, prevents Hb decline and may ameliorate deterioration in QOL during chemotherapy in these patients. In addition to studies evaluating early intervention with epoetin alfa, several ongoing studies are examining new epoetin alfa dosages and administration schedules in an effort to optimize Hb correction. For example, investigators are evaluating whether regimens with high initial dosages (60 000–80 000 IU QW) of epoetin alfa, given for a short period of time, may improve hematologic response in patients with established anemia and whether less frequent maintenance dosing (i.e., 120 000 IU every 3 weeks) is sufficient to maintain the Hb response. If high initial epoetin alfa doses followed by infrequent maintenance dosing proves effective in larger clinical trials, a variety of more convenient dosing regimens may be available.

Keywords: Anemia; Epoetin alfa dosing; Chemotherapy; Quality of life

1. Introduction

The management of cancer and treatment-related anemia has been addressed in both anemia- and disease-specific cancer treatment guidelines [1,2] as the impact of anemia is recognized. Anemia is a common consequence of cancer and cancer-related treatment. In a survey of patients receiving radiation or chemoradiation, approximately 48% of patients have hemoglobin (Hb) levels <12 g/dl upon presentation; during the course of therapy, the prevalence may be as high as 82%, depending on the type of cancer and the regimens involved [3]. In the majority of cases, anemia is mild to moderate (Hb: 9.0–11.9 g/dl) [3] and was thought to be of little consequence prior to the association with diminished quality of life (QOL) [4,5]. Anemia causes a wide spectrum of signs and symptoms ranging from fatigue to cognitive dysfunction, headache, dizziness, chest pain, dyspnea, digestive problems, edema, and heart failure [4,6]. Fatigue has been reported to affect 30% of patients on a daily basis and 59% of patients at least weekly [5]. It is now well recognized that cancer-related fatigue is a definable, multifactorial entity and anemia with fatigue fits under a much larger QOL construct with many complex causes. Fatigue may impair a

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patient's psychological, social, economic, and physical well-being, both during the initial treatment and for years afterward [5]. Multiple studies are underway to ascertain the effects of anemia on treatment outcome in patients receiving chemotherapy, radiation therapy, or both.

The primary therapeutic options for reversing anemia are blood transfusions and administration of recombinant human erythropoietin (rHuEPO, epoetin alfa). The National Comprehensive Cancer Network (NCCN) guidelines reiterated the point that blood transfusions remain the treatment of choice when immediate correction of anemia is required [2]. In recent years, use of this approach for moderate anemia has been limited by an appreciation of the associated risks, such as infection, nonhemolytic and hemolytic transfusion reactions, iron overload, reduced immunocompetence (although the clinical significance of this is unknown), and shortages in the blood supply [2,7]. As a result, the transfusion "trigger" i.e.—the level to which Hb must fall before the patient receives a transfusion—may be as low as 7–8 g/dl in some institutions [2].

Mild to moderate anemia is generally treated with rHuEPO rather than transfusion, and its use has been addressed in guidelines issued by the American Society of Hematology and the American Society of Clinical Oncology (ASH/ASCO) and by the NCCN (1,2). Clinical trials have shown that epoetin alfa, in thrice-weekly (TIW) regimens of 10 000–20 000 IU or 150–300 IU/kg, produces a consistent Hb correction of approximately 1 g/dl at week 4 and approximately 2 g/dl at week 8 [8–10]. Response rates (defined as Hb increase of $\geqslant 2$ g/dl or achievement of Hb level $\geqslant 12$ g/dl without transfusion) are approximately 70–74%, with appropriate dose escalation if required [9,10]. Moreover, according to a large meta-analysis, epoetin alfa reduces the percentage of patients who require transfusion by 9–45% in patients with a mean baseline Hb level of <10 g/dl; by 7–47% in patients whose Hb levels are between 10 g/dl and 12 g/dl; and by 7–39% in patients with baseline Hb levels >12 g/dl [11]. These increases in Hb levels have been associated with statistically significant improvements in QOL [9,10]. A recent study that compared clinical trial QOL data obtained using the Functional Assessment of Cancer Therapy-Anemia (FACT-An) with normative FACT-An data for the general population has shown that the epoetin-alfa–related improvements in QOL measured by this instrument were clinically meaningful, as well as statistically significant [10,12]. (The FACT-An is a 55-item questionnaire consisting of a 34-item general questionnaire, the FACT-G, and a 21-item Anemia subscale. Thirteen of the 21 anemia items comprise a separate fatigue subscale [10]. It is a QOL instrument now used extensively in clinical studies involving cancer patients.) Generally, epoetin alfa has been well tolerated.

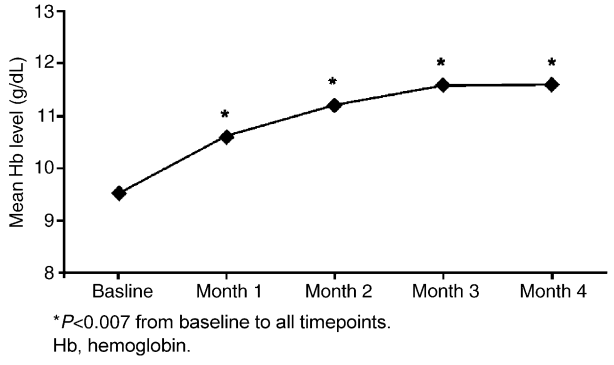

Fig. 1. Mean Hb levels in 2964 cancer patients treated with epoetin alfa 40 000–60 000 IU once weekly. Adapted with permission [13].

2. Less frequent dosing

Recommendations for use of epoetin alfa made by ASH/ASCO were primarily derived from studies in which epoetin alfa was administered TIW in dosages of 150–300 IU/kg [1]. The NCCN guidelines also include the more convenient once-weekly (QW) 40 000–60 000 IU epoetin alfa regimen [2].

Data supporting the widely used QW epoetin alfa regimen of 40 000–60 000 IU subcutaneously (s.c.) are found in three clinical studies. The first was a prospective, multicenter, open-label, nonrandomized, community-based trial involving 2964 evaluable patients who were receiving chemotherapy for various solid and hematologic malignancies [13]. The mean baseline Hb level was 9.5 g/dl, and all patients were anemic (Hb <11 g/dl). Epoetin alfa was administered sc QW in a dose of 40 000 IU, which was increased to 60,000 IU after 4 weeks if Hb levels did not increase by $\geqslant 1$ g/dl. This QW regimen of epoetin alfa increased mean Hb levels by 1.1 g/dl at week 4 and by 1.8 g/dl at study end (Fig. 1) ($P<0.007$ for difference in Hb level from baseline at all evaluation points, including week 4). The significant increase ($P<0.007$) in Hb level occurred across all major tumor types. The overall hematopoietic response rate (defined as an Hb increase of $\geqslant 2$ g/dl or an achieved Hb of $\geqslant 12$ g/dl during the study, with no transfusions) was 68%. The FACT-An and Linear Analog Scale Assessment (LASA) measures of QOL both demonstrated significant improvements ($P<0.001$), which were associated with increased Hb levels.

Results have been reported from a second prospective, open-label, community-based trial in which QW doses of epoetin alfa (40 000–60 000 IU) were administered to 442 patients receiving chemoradiotherapy [14]. Similar increases in Hb of 1.1 g/dl at week 4 and 2.2 g/dl at study end were seen and were significant ($P<0.05$) compared with baseline at week 4 and at all evaluation points thereafter. The overall response rate was 74% (Table 1).

Table 1
Overview of dosage regimens of epoetin alfa: effects on Hb levels and response rates in recent clinical trials

Author/year	*N*	Dosage regimen of epoetin alfa	Mean baseline Hb (g/dl)	Mean Hb increase at 4 weeks (g/dl)	Mean Hb increase at 8 weeks (g/dl)	Mean final Hb increase (g/dl)	Response rate (%)
Littlewood, 2001 [10]	375	150–300 IU/kg TIW for 12–24 weeks	9.9	0.9	1.8	2.2*	70.5[a]
Gabrilove, 2001 [13]	2964	40 000–60 000 IU QW for 16 weeks	9.5	1.1	1.7	1.8*	68[b]
Chap, 2002 [20][c]	11	60 000 IU QW for 16 weeks	9.1	1.1	2.6	1.7	NA
O'Shaughnessy, 2002 [18][c]	93	40 000 IU QW for 12 weeks	>12	0.5	0.6	0.8*	NA
Sloan, 2002 [15]	344	40 000–60 000 IU QW for 16 weeks	<11.5 for males <10.5 for females	NA	NA	NA	NA
Straus, 2002 [19][c]	179	40 000 IU QW for 16 weeks	12.4	NA	NA	0.8*	NA
Hudis, 2003 [16]	1597	40 000–60 000 IU QW for up to 24 weeks	12.3	NA	NA	1.2*	NA
Patton, 2003 [21]	20	60 000 IU QW for 8 weeks, then 120 000 IU Q3W for 16 weeks	10.0	1.1	2.8	3.0	NA
Shasha, 2003 [14]	442	40 000–60 000 IU QW for 16 weeks	9.9	1.1	1.7	2.2*	74[b]

BIW, twice weekly; Hb, hemoglobin; NA, not available; QW, once weekly; Q3W, every 3 weeks; TIW, thrice weekly. *$P<0.05$ versus baseline.
[a] Response defined as an increase in Hb ⩾2 g/dL or achievement of an Hb ⩾12 g/dL during the study, with no transfusions given within the previous 30 days.
[b] Response defined as a ⩾2 g/dL increase in Hb unrelated to transfusion.
[c] Interim analysis.

Recently, a randomized, multicenter, double-blind, placebo-controlled study enrolled 344 anemic (baseline Hb ⩽11.5 g/dl and ⩽10.5 g/dl for males and females, respectively) patients with advanced cancer receiving chemotherapy and epoetin alfa at 40 000–60 000 IU QW, with transfusion reduction as the primary endpoint. The need for transfusions was reduced, with 12% of patients in the epoetin alfa group requiring at least one transfusion during the 4-month study period versus 27% of patients in the placebo arm ($P=0.0008$) [15]. These results are consistent with the transfusion rate reductions observed in the recent major TIW dosing study in which 24.7% of patients in the epoetin alfa treatment group versus 39.5% of those in the placebo group required at least one transfusion after day 28 ($P=0.0057$) [10].

3. Early intervention

Current clinical guidelines for anemia management note that the evidence supporting the use of epoetin alfa is strongest for patients whose Hb levels are ⩽10 g/dl [1,2]. The available published, randomized, controlled trials at the time of the guideline development did not have sufficient numbers of patients in the Hb 10–12-g/dl group to evaluate the benefit of early intervention; this has prompted the initiation of several studies to address this endpoint, which have now been reported in abstract form.

In a phase IV, open-label, nonrandomized, multicenter study, Hudis and colleagues [16] studied the effects of epoetin alfa (40 000–60 000 IU QW up to 24 weeks) on Hb levels and QOL parameters in patients with early-stage breast cancer. Final analyses were based on data from 1597 evaluable patients. At baseline, the mean Hb level was 12.3 g/dl and impairment of QOL was minimal. Despite institution of adjuvant chemotherapy, mean Hb levels had increased by 1.2 g/dl ($P<0.05$) by end of study. In a similar, historical-comparison population who did not receive epoetin alfa, mean Hb levels decreased by 2.0 g/dl [17]. Epoetin alfa was well tolerated in this patient group.

Similarly, O'Shaughnessy *et al.* [18] conducted a double-blind, randomized, placebo-controlled pilot trial of epoetin alfa, 40 000 IU QW, in 94 breast cancer patients undergoing four cycles of adjuvant or neo-adjuvant chemotherapy over 3 months. The mean baseline Hb level was ~12 g/dl. The mean changes in Hb from baseline to cycle 4 were an increase of 0.8 g/dl in the epoetin alfa group, compared with a decrease of 2.1 g/dl in the placebo group ($P<0.001$). The QOL measures (LASA and FACT-An) suggested that the epoetin alfa group had greater improvement of cognitive function ($P=0.011$ at cycle 4, as measured by the Executive Interview [EXIT25]) and less QOL impairment. These results suggest that early intervention with epoetin alfa can maintain or increase Hb levels and may maintain or improve QOL and cognitive function in breast cancer patients during chemotherapy.

An interim report from a randomized, multicenter, open-label trial by Straus *et al.* [19] showed increased Hb levels and improved QOL with epoetin alfa QW in patients with mild anemia. Among 179 of 260 enrolled patients with lymphoma (92%), chronic lymphocytic leukemia (4%), or multiple myeloma (5%) receiving chemotherapy, 77 were randomized to receive immediate treatment with epoetin alfa 40 000 IU QW at the start

of chemotherapy, while 102 were randomized to observation during chemotherapy, with epoetin alfa 40 000 IU QW to be given if Hb declined to <9 g/dl. Baseline Hb levels (12.4 ± 1.4 g/dl) increased significantly in the immediate-treatment group (0.8 ± 2.5 g/dl, $P = 0.007$) and decreased significantly in the observation group (-0.8 ± 1.0 g/dl, $P < 0.001$; between-group, $P = 0.005$). The immediate-treatment group reported significant improvements in QOL as measured by total FACT-An ($P = 0.036$) as well as by the anemia ($P = 0.047$), physical well-being ($P = 0.003$), and fatigue ($P = 0.032$) subscales of the FACT-An; changes in total FACT-An and anemia subscale scores were significantly correlated with change in Hb levels, despite the small magnitude of Hb change ($r = 0.020$; $P < 0.05$). Immediate treatment with epoetin alfa at the start of chemotherapy also resulted in a decreased number of clinic visits ($P = 0.002$). These interim results suggest that QW epoetin alfa benefits Hb levels and QOL in patients with mild anemia receiving chemotherapy for hematologic malignancies.

4. Optimization of dosing regimens

Other studies are evaluating higher QW doses of epoetin alfa to determine whether the overall Hb response can be improved. In an open-label, nonrandomized pilot study, Chap *et al.* [20] are evaluating epoetin alfa therapy at a dosage of 60 000 IU QW for up to 16 weeks in patients receiving chemotherapy. The dosage is reduced to 40 000 IU QW if the Hb increases by >1.3 g/dl over a 2-week period. Therapy is withheld if the Hb level increases to >15 g/dl and is resumed when the Hb decreases to 13 g/dl. Results are currently available for 11 patients (mean baseline Hb: 9.1 ± 1.0 g/dl). The mean increases in Hb levels in this group were 1.1 ± 1.5 g/dL at week 4 and 2.6 ± 2.4 g/dL at week 8. A randomized comparison is required to determine whether this Hb response is better than that achieved with more conventional dosing. No adverse events were reported.

In another open-label, nonrandomized pilot study, Patton and colleagues [21] administered epoetin alfa at a starting dosage of 60 000 IU QW for approximately 2 months to patients undergoing chemotherapy. Thereafter, if Hb levels increased by $\geqslant 2$ g/dl above baseline, a maintenance dose of 120 000 IU was administered once every 3 weeks. If Hb levels increased by >1.3 g/dl in a 2-week period, the dosage was decreased to 40 000 IU QW. If Hb levels increased to >15 g/dl at any time during the study, therapy was withheld until Hb levels decreased to $\leqslant 13$ g/dl and then resumed at 20 000 IU QW. The total treatment period was 24 weeks. Data have been obtained for 20 patients with nonmyeloid malignancies and a mean baseline Hb of 10.0 ± 0.8 g/dl. Mean increase in Hb was 1.1 g/dl at 4 weeks and 2.8 g/dl at 8 weeks. Mean increase in Hb from baseline to last measurement was 3.0 g/dl. Epoetin alfa was well tolerated. Larger-scale trials evaluating this dosing regimen are warranted.

5. Summary

Clinical guidelines are evolving with recommendations for the use of rHuEPO for the treatment of patients with moderate anemia. Most of the original data for epoetin alfa usage was based on 150–300 IU/kg TIW regimens, which consistently increased Hb levels by approximately 1 g/dl at 4 weeks and 2 g/dl at 8 weeks, with overall response rates in the 68–74% range using appropriate dosing escalation. In addition, open-label community-based and double-blind, randomized clinical trials in more than 3000 patients have documented similar results with a QW epoetin alfa regimen of 40 000–60 000 IU.

Ongoing research is exploring the effects of administering epoetin alfa therapy to cancer patients with mild to moderate anemia. Initial results of these early intervention studies indicate that this approach maintains normal Hb levels while stabilizing or improving QOL and cognitive function in patients receiving chemotherapy. These findings have implications for the target Hb levels to be used for the initiation of epoetin alfa, as well as the anemia management goals of this therapy, including reduction of transfusion requirements and potential avoidance of the deteriorating QOL and physical well-being associated with anemia.

Interesting results have also been obtained from small studies evaluating higher starting doses of epoetin alfa followed by less frequent maintenance doses to optimize response time and minimize frequency of administration. Randomized studies are essential and are underway to evaluate optimal doses, schedules, and thresholds for initiation of treatment.

References

1. Rizzo JD, Lichtin AE, Woolf SH, *et al.* Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *Blood* 2002, **100**, 2303–2320.
2. National Comprehensive Cancer Network. *Clinical practice guidelines in oncology: cancer and treatment-related anemia v.1.2003*. Rockledge, PA, NCCN, 2003.
3. Harrison LB, Shasha D, White C, Ramden B. Radiotherapy-associated anemia: the scope of the problem. *Oncologist* 2000, **5**(Suppl. 2), 1–7.
4. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol* 1998, **25**(Suppl. 7), 43–46.
5. Curt GA. The impact of fatigue on patients with cancer: overview of FATIGUE 1 and 2. *Oncologist* 2000, **5**(Suppl. 2), 9–12.
6. Ludwig H, Strasser K. Symptomatology of anemia. *Semin Oncol* 2001, **28**(Suppl. 2), 7–14.

7. Goodnough LT, Brecher ME, Kanter MH, *et al*. Transfusion medicine. First of two parts—blood transfusion. *N Engl J Med* 1999, **340**, 438–447.
8. Glaspy J, Bukowski R, Steinberg D, Taylor C, Tchekmedyian S, Vadhan-Raj S, for the Procrit Study Group. Impact of therapy with epoetin alfa on clinical outcomes in patients with non-myeloid malignancies during cancer chemotherapy in community oncology practice. *J Clin Oncol* 1997, **15**, 1218–1234.
9. Demetri GD, Kris M, Wade J, Degos L, Cela D, for the Procrit Study Group. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. *J Clin Oncol* 1998, **16**, 3412–3425.
10. Littlewood TJ, Bajetta E, Nortier JWR, Vercammen E, Rapoport B, for the Epoetin Alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001, **11**, 2865–2874.
11. Seidenfeld J, Piper M, Flamm C, *et al*. Epoetin treatment of anemia associated with cancer therapy: a systematic review and meta-analysis of controlled clinical trials. *J Natl Cancer Inst* 2001, **93**, 1204–1214.
12. Cella D, Zagari MJ, Vandoros C, Gagnon DD, Hurtz HH, Nortier JW. Epoetin alfa treatment results in clinically significant improvements in quality of life in anemia cancer patients when referenced to the general population. *J Clin Oncol* 2003, **21**, 366–373.
13. Gabrilove JL, Cleeland CS, Livingston ARB, Sarokhan B, Winer E, Einhorn LH. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol* 2001, **19**, 2875–2992.
14. Shasha D, George MJ, Harrison LB. Once-weekly dosing of epoetin-α increases hemoglobin and improves quality of life in anemic cancer patients receiving radiation therapy either concomitantly or sequentially with chemotherapy. *Cancer* 2003, **98**, 1072–1079.
15. Sloan JA, Witzig T, Silberstein P, *et al*. Quality of life, blood transfusions, and toxicity, in anemic patients with advanced cancer receiving weekly erythropoietin while on chemotherapy: results from a phase III randomized double-blind placebo-controled study. *Blood* 2002, **100**, 287a (abstr 1103).
16. Hudis C, Williams D, Gralow J, for the PROCRIT Study Group. Epoetin alfa maintains hemoglobin and quality of life in breast cancer patients receiving conventional adjuvant chemotherapy: final report. *Proc Soc Clin Oncol* 2003, **22**, 767 (abstr 3084).
17. Lawless GD, Ford JM. Cumulative prevalence of anemia in early-stage breast cancer (ESBC) patients. *Blood* 2000, **96**, 390b (abstr 5446).
18. O'Shaughnessy J, Vukelja S, Savin M, *et al*. Impact of epoetin alfa on cognitive function, asthenia, and quality of life in women with breast cancer receiving adjuvant or neoadjuvant chemotherapy: analysis of 6-month follow-up data. *Breast Cancer Res Treat* 2002, **76**(Suppl. 1), S138 (abstr 550).
19. Straus DJ, Turner RR, Testa MA, Hayes JF, Sarokhan BJ, the Procrit Hematologic Malignancies Study Group. Epoetin alfa treatment improves quality of life and increases hemoglobin levels during chemotherapy for lymphoma, chronic lymphocytic leukemia (CLL), and multiple myeloma (MM) patients with mild-to-moderate anemia. *Blood* 2002, **100**, 220a–2221 (abstr. 828).
20. Chap L, George M, Glaspy JA. Evaluation of epoetin alfa (Procrit®) 60,000 U once weekly in anemia cancer patients receiving chemotherapy. *Proc Am Soc Clin Oncol* 2002, **21**, 264b (abstr. 2873).
21. Patton J, Camp M, Kuzur M, *et al*. Epoetin alfa 60,000 U once weekly followed by 120,000 U every 3 weeks maintains hemoglobin levels in anemic cancer patients receiving chemotherapy: final report. *Proc Soc Clin Oncol* 2003, **22**, 754 (abstr 3033).